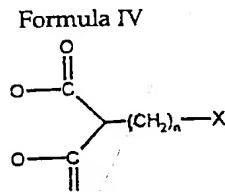
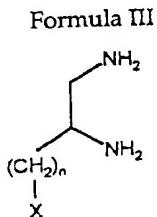
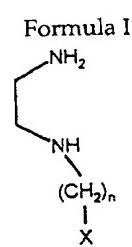


## Claims

1. Transferrin, albumin and polyethylene glycol conjugates, obtainable by coupling a  
2 derivatized cytostatic compound, consisting of the cytostatic compound and a  
3 spacer molecule having a maleimide group, to thiolated transferrin or albumin  
4 having on the average from 1 to 30 HS groups or to polyethylene glycol having, at  
5 least, one HS or H<sub>2</sub>N group and having a mass of about between 5,000 and  
6 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic  
7 compounds are bound to one molecule of transferrin, albumin or polyethylene  
8 glycol,  
9 or by coupling a derivatized cytostatic compound, consisting of the cytostatic  
10 compound and a spacer molecule having a N-hydroxysuccinimide ester group, to  
11 thiolated transferrin or albumin having on the average from 1 to 30 HS groups or  
12 to the polyethylene glycol having, at least, one HO- or H<sub>2</sub>N- group and having a  
13 mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30  
14 molecules of the derivatized cytostatic compounds are bound to one molecule of  
15 transferrin, albumin or polyethylene glycol,  
16 or obtainable by loading thiolated albumin with from 2 to 30 equivalents of the  
17 derivatized cytostatic compound, consisting of the cytostatic compound and a  
18 spacer molecule having a maleimide group, and conjugating with transferrin or a  
19 monoclonal antibody which is directed against a tumor-associated antigen, via a  
20 bismaleimide compound.
1. Transferrin, albumin and polyethylene glycol conjugates according to claim 1,  
2 obtainable by coupling a derivatized cytostatic compound, consisting of a  
3 cytostatic compound from the group of the anthracyclines, the nitrogen mustard  
4 gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the  
5 taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids  
6 or the *cis*-configured platinum(II)-complexes, respectively, and a spacer molecule  
7 having a maleimide group, to thiolated transferrin or albumin having on the

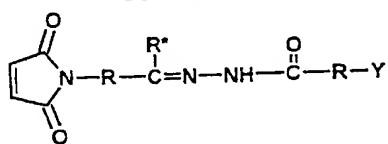
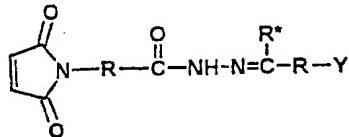
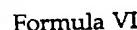
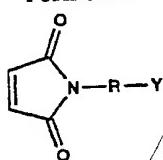
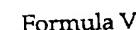
average from 1 to 30 HS groups or to polyethylene glycol having, at least, one HS or H<sub>2</sub>N group and having a mass of about between 5,000 and 200,000 Da, wherein about from 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol, or by coupling a derivatized cytostatic compound, consisting of the cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vincan alkaloids or the *cis*-configured platinum(II)-complexes and a spacer molecule having a N-hydroxysuccinimide ester group, to thiolated transferrin or albumin having on the average from 1 to 30 HS groups or to the polyethylene glycol having, at least, one HO- or H<sub>2</sub>N- group and having a mass of about between 5,000 and 200,000 Da, wherein about form 1 to 30 molecules of the derivatized cytostatic compounds are bound to one molecule of transferrin, albumin or polyethylene glycol, or by loading thiolated albumin with from 2 to 30 equivalents of the derivatized cytostatic compound, consisting of the cytostatic compound from the group of the anthracyclines, the nitrogen mustard gas derivatives, the purine or pyrimidine antagonists, the folic acid antagonists, the taxoids, the camptothecines, the podophyllotoxin derivatives, the vinca alkaloids or the *cis*-configured platinum(II)-complexes, respectively, and a spacer molecule having a maleimide group, and conjugating with transferrin or a monoclonal antibody, which is directed against a tumor-associated antigen, via a bismaleimide compound.

3. Transferrin, albumin and polyethylene glycol conjugates, according to anyone of the preceding claims, obtainable by reacting
  - a). doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxandrone, chlorambucil, melphalan, 5-fluorouracil, 5'-desoxy-5-fluorouridine, thioguanine, methotrexate, paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide, mitopodazole, vinblastine, vincristine, vindesine, vinorelbine or a compound of the general formula I, II, III or IV:



$n = 0 - 6$ ,  $X = -\text{NH}_2$ ,  $-\text{OH}$ ,  $-\text{COOH}$ ,  $-\text{O}-\text{CO-R-COR}^*$ ,  $-\text{NH-CO-R-COR}^*$ , wherein R is an aliphatic carbon chain with 1 - 6 carbon atoms or a substituted or unsubstituted phenylene group and  $R^*$  is H, phenyl, alkyl with 1 - 6 carbon atoms, and the amine functions are provided with a protective group such as the *tert*.-butyloxycarbonyl protective group,

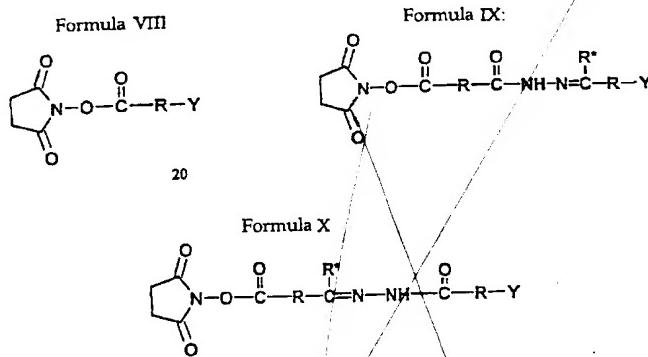
with a maleinimide compound of the general formula V, VI or VII



wherein, in the case that R is an aliphatic carbon chain with 1 - 6 carbon atoms, Y = -OH, -COOH, -COCl, -CONH-(CH<sub>2</sub>)<sub>n</sub>-OH, -COO-(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, -COO-(CH<sub>2</sub>)<sub>n</sub>-NHNH<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>3</sub>Cl, -SO<sub>2</sub>-NHNH<sub>2</sub>, -O-COCl, -CHO, COR\* with n = 1 - 6 and R\* = H, phenyl, alkyl with 1 - 6 carbon atoms, and wherein, in the case that R

18       is a substituted or unsubstituted benzyl group or a substituted or unsubstituted  
 19       phenylene group, Y = -OH, -COOH, -COCl, -CONH-(CH<sub>2</sub>)<sub>n</sub>-OH, -COO-(CH<sub>2</sub>)<sub>n</sub>-  
 20       NH<sub>2</sub>, -COO-(CH<sub>2</sub>)<sub>n</sub>-NHNH<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>3</sub>Cl, -SO<sub>2</sub>-NHNH<sub>2</sub>, -O-COCl, -CHO, -  
 21       COR\*, -CO-NHNH<sub>2</sub> with n = 1 - 6 and R\* = H, phenyl, alkyl with 1 - 6 carbon  
 22       atoms,

23       or with an N-hydroxysuccinimide compound of the general formula VIII, IX or X



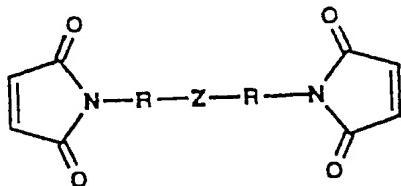
24       wherein R is a substituted or unsubstituted phenylene group, Y = -OH, -NH<sub>2</sub>, -  
 25       NHNH<sub>2</sub>, -COOH, -COCl, -COO-(CH<sub>2</sub>)<sub>n</sub>-OH, -CONH-(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, -COO-(CH<sub>2</sub>)<sub>n</sub>-  
 26       NHNH<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>3</sub>Cl, -SO<sub>2</sub>-NHNH<sub>2</sub>, -O-COCl, -CHO, -COR\*, -CO-NHNH<sub>2</sub>  
 27       with n = 1 - 6 and R\* = H, phenyl, alkyl with 1 - 6 carbon atoms,  
 28       wherein, in the derivatives obtained from the compounds of the general formula I,  
 29       II or III, the protective group is removed and the thus-obtained amines are reacted  
 30       with a tetrachloroplatinate salt to yield the corresponding *cis*-configured  
 31       platinum(II)-complexes, and wherein the derivatives obtained from the  
 32       compounds of the general formula IV are reacted with *cis*-[PtA<sub>2</sub>B] (A = halogen,  
 33       B = (NH<sub>3</sub>)<sub>2</sub>, ethylene diamine, propane diamine, 1,2-diaminocyclohexane) to yield  
 34       the corresponding platinum(II)-complexes,  
 35       so that maleinimide derivatives or N-hydroxysuccinimide ester derivatives of  
 36       cytostatic compounds are provided, wherein the chemical linkage occurs between

37       the cytostatic compound and the maleimide compound or N-  
38       hydroxysuccinimide compound, respectively, through an amide, ester, imine,  
39       hydrazone, carboxylhydrazone, oxycarbonyl, acetal or ketal bond, and

40       b). the thus-obtained maleimide derivative is coupled to thiolated transferrin or  
41       albumin with on the average from 1 to 30 HS groups or to polyethylene glycol  
42       having, at least, one HS- or H<sub>2</sub>N group and having a mass of between about 5,000  
43       and 200,000 Da, wherein about from 1 to 30 molecules of the maleimide  
44       derivatives obtained in Step a) are bound to one molecule of transferrin, albumin  
45       or polyethylene glycol,

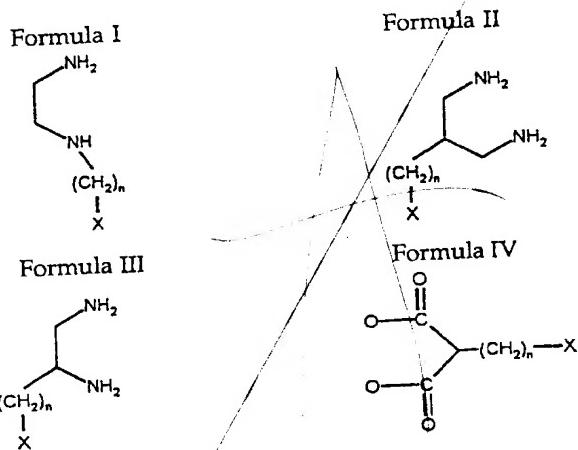
46       or the thus-obtained N-hydroxysuccinimide ester derivative is coupled to  
47       transferrin or albumin or to polyethylene glycol having, at least, one HO- or H<sub>2</sub>N  
48       group, having a mass of between approximately 5,000 and 200,000 Da, wherein  
49       about 1 to 30 molecules of the N-hydroxysuccinimide derivatives obtained in Step  
50       a) are bound to one molecule of transferrin, albumin or polyethylene glycol,

51       or by loading thiolated albumin with from 2 to 30 equivalents of the maleimide  
52       derivatives obtained in Step a) and conjugating with transferrin or a monoclonal  
53       antibody which is directed against a tumor-associated antigen, via a  
54       bismaleimide compound of the general formula XI



55       Z = -CO-NH-(CH<sub>2</sub>)<sub>n</sub>-NH-CO-, -CO-O-(CH<sub>2</sub>)<sub>n</sub>-O-CO-, -C=NH-(CH<sub>2</sub>)<sub>n</sub>-NH=C-, -  
56       C=N-NH-(CH<sub>2</sub>)<sub>n</sub>-NH-N=C-, -C=N-NH-CO-(CH<sub>2</sub>)<sub>n</sub>-CO-NH-N=C-, n = 2 - 12.

- 1           4. Method for the production of transferrin, albumin and polyethylene glycol  
 2           conjugate, according to anyone of the preceding claims, characterized in that  
 3           a). doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxandrone, chloroambucil,  
 4           melphalan, 5-fluorouracyl, 5'-desoxy-5-fluorouridine, thioguanine, methotrexate,  
 5           paclitaxel, docetaxel, topotecane, 9-aminocamptothecine, etoposide, teniposide,  
 6           mitopodoside, vinblastine, vincristine, vindesine, vinorelbine or a compound of  
 7           general the formula I, II, III or IV:

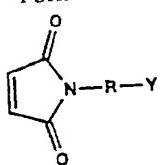


8           n = 0 - 6, X = -NH<sub>2</sub>, -OH, -COOH, -O-CO-R-COR\*, -NH-CO-R-COR\*, wherein  
 9           R is an aliphatic carbon chain with 1 - 6 carbon atoms or a substituted or  
 10          unsubstituted phenylene group and R\* is H, phenyl, alkyl with 1 - 6 carbon  
 11          atoms, and the amine functions are provided with a protective group such as the  
 12          *tert.*-butyloxycarbonyl protective group,

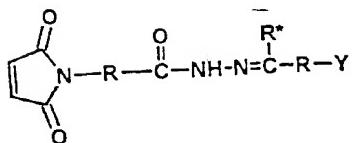
13          with a maleimide compound of the general formula V, VI or VII

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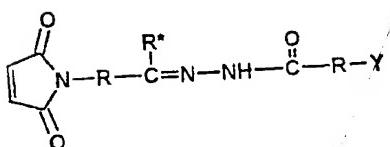
Formula V



Formula VI



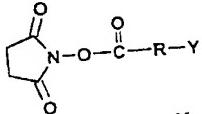
Formula VII



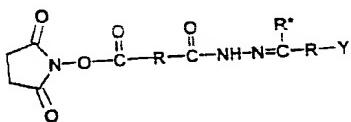
wherein, in the case that R is an aliphatic carbon chain with 1 - 6 carbon atoms,  
 Y = -OH, -COOH, -COCl, -CONH-(CH<sub>2</sub>)<sub>n</sub>-OH, -COO-(CH<sub>2</sub>)<sub>n</sub>-NH<sub>2</sub>, -COO-(CH<sub>2</sub>)<sub>n</sub>-  
 NHNH<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>3</sub>Cl, -SO<sub>2</sub>-NNHNH<sub>2</sub>, -O-COCl, -CHO, -COR\* with n = 1 - 6  
 and R\* = H, phenyl, alkyl with 1 - 6 carbon atoms, and wherein, in the case that R  
 is a substituted or unsubstituted benzyl group or a substituted or unsubstituted  
 phenylene group, Y = -OH, -COOH, -COCl, -CONH-(CH<sub>2</sub>)<sub>n</sub>-OH, -COO-(CH<sub>2</sub>)<sub>n</sub>-  
 NH<sub>2</sub>, -COO-(CH<sub>2</sub>)<sub>n</sub>-NNHNH<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>3</sub>Cl, -SO<sub>2</sub>-NNHNH<sub>2</sub>, -O-COCl, -CHO, -  
 COR\* with n = 1 - 6 and R\* = H, phenyl, alkyl with 1 - 6 carbon atoms,

or with an N-hydroxysuccinimide compound of the general formulas VIII, IX or X

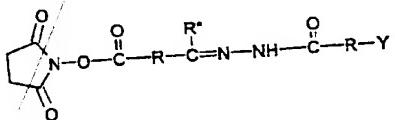
Formula VIII



Formula IX:



Formula X

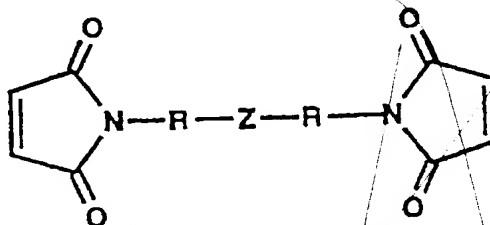


25                   NHNH<sub>2</sub>, -SO<sub>3</sub>H, -SO<sub>3</sub>Cl, -SO<sub>2</sub>-NHNH<sub>2</sub>, -O-COCl, -CHO, -COR\*, -CO-NHNH<sub>2</sub>  
26                   with n = 1 - 6 and R\* = H, phenyl, alkyl with 1 - 6 carbon atoms,  
27                   wherein, in the derivatives obtained from the compounds of the general formula I,  
28                   II or III, the protective group is removed and the thus-obtained amines are reacted  
29                   with a tetrachloroplatinate salt to yield the corresponding *cis*-configured  
30                   platinum(II)-complexes, and wherein the derivatives obtained from the  
31                   compounds of the general formula IV are reacted with *cis*-[PtA<sub>2</sub>B] (A = halogen,  
32                   B = (NH<sub>3</sub>)<sub>2</sub>, ethylene diamine, propane diamine, 1,2-diaminocyclohexane) to yield  
33                   the corresponding platinum(II)-complexes,

34                   so that maleimide derivatives or N-hydroxysuccinimide ester derivatives of  
35                   cytostatic compounds are provided, wherein the chemical linkage occurs between  
36                   the cytostatic compound and the maleimide compound or N-  
37                   hydroxysuccinimide compound through an amide, ester, imine, hydrazone,  
38                   carboxyhydrazone, oxycarbonyl, acetal or ketal bond, and

- 39                   b.) the thus-obtained maleimide derivative is coupled to thiolated transferrin or  
40                   albumin having from 1 to 30 HS groups on the average or to polyethylene glycol  
41                   having, at least, one HS- or H<sub>2</sub>N group and having a mass of between about 5,000  
42                   and 200,000 Da, wherein about from 1 to 30 molecules of the maleimide  
43                   derivatives obtained in Step a) are bound to one molecule of transferrin, albumin  
44                   or polyethylene glycol,  
45                   or the thus-obtained N-hydroxysuccinimide ester derivative is coupled to  
46                   transferrin or albumin or to polyethylene glycol having, at least, one HO- or H<sub>2</sub>N  
47                   group, having a mass of between approximately 5,000 and 200,000 Da, wherein  
48                   about from 1 to 30 molecules of the N-hydroxysuccinimide derivatives obtained  
49                   in Step a) are bound to one molecule of transferrin, albumin or polyethylene  
50                   glycol,

51 or by loading thiolated albumin with from 2 to 30 equivalents of the maleimide  
52 derivatives obtained in Step a) and conjugating with transferrin or a monoclonal  
53 antibody which is directed against a tumor-associated antigen, via a  
54 bismaleimide compound of the general formula XI



55  $Z = -CO-NH-(CH_2)_n-NH-CO-, -CO-O-(CH_2)_n-O-CO-, -C=NH-(CH_2)_n-NH=C-, -$   
56  $C=N-NH-(CH_2)_n-NH-N=C-, -C=N-NH-CO-(CH_2)_n-CO-NH-N=C-, n = 2 - 12.$

- 1 5. Pharmaceutical composition containing a compound according to anyone of the  
2 claims 1 to 3 optionally together with usual carriers and auxiliary agents.
- 1 6. Use of the transferrin, albumin and polyethylene glycol conjugates according to  
2 anyone of the claims 1 to 3 for the treatment of cancer diseases.

A1D  
A2